

Comments of Robert T. Croyle, Ph.D. (Director, Division of Cancer Control and Population Sciences, National Cancer Institute)

Comment 1:

The California EPA's report on Environmental Tobacco Smoke (ETS) as a Toxic Air Contaminant provides an excellent discussion of findings on the health effects of ETS. The Division of Cancer Control and Population Sciences of the National Cancer Institute appreciates the opportunity to review and comment on this report. The authors of the report should be congratulated on this achievement. The California EPA's previous report has served as an authoritative reference document on ETS and health effect, and this new report is likely to become widely read and cited. Two important changes in the new report are the designation of ETS as causes of nasal and breast cancers. This is in contrast to the findings of the International Agency for Research (IARC) in 2002. Although the IARC report in the monograph series Evaluation of the Carcinogenic Risks to Humans, Tobacco Smoke and Involuntary Smoking, Volume 83 is not yet published in book form, the summary conclusions are available at the agency's website: <http://monographs.iarc.fr/htdocs/indexes/vol83index.html>. In view of the differences between the conclusions of two reports and the public health implications of the new designations by the California EPA of ETS as causal factors in the etiology of particular cancers, the National Cancer Institute, part of the National Institutes of Health, strongly recommends the appointment by the California EPA of an expert panel representing the appropriate disciplines to review and to come to a consensus on the evidence on ETS and cancer.

Response:

Thank you for your comments. Our document is peer reviewed by the State's Scientific Review Panel on Toxic Air Contaminants, a body created under state law to provide independent scientific review of documents produced by CalEPA. It is composed of 9 independent scientists nominated by the President of the University of California from the disciplines of pathology, oncology, epidemiology, biostatistics, toxicology, occupational medicine, atmospheric chemistry, biochemistry and molecular biology, and other relevant disciplines. They consider both the document prepared by ARB and OEHHA as well as all the public comments and responses to those comments as part of the peer review process. If the Panel wishes they may consult additional experts during their review process.

There are a number of reasons why the conclusions of the Cal/EPA report may differ from other evaluations, such as that recently published by IARC. In the case of the association with breast cancer, we were able to include some studies and meta-analyses that were unavailable to IARC

at the time of their review. OEHHA staff and consultants also undertook different (and more extensive) analyses of data than those used by IARC

The designation as a causal factor for nasal sinus cancer is not a new finding and was found originally in the 1997 document (CA EPA, 1997). As noted below in the response to comment two, we have now separated nasopharyngeal cancer into a separate section with findings distinct from those of nasal sinus cancer.

Some specific comments on Chapter 7 Carcinogenic Effects:

Section 7.3.1 Nasal sinus cancer

Comment 2:

The studies listed under nasal sinus cancer appear to be for nasopharyngeal cancer, a different anatomic site than nasal cancer, a term that typically refers to cancers of the nose and paranasal sinuses.

Response:

The comment is correct and the text has been changed to reflect the different cancer sites. There are no new studies specifically addressing nasal sinus cancer to alter the conclusion in the 1997 document of an association with ETS exposure. Nasopharyngeal is now listed as a separate category with the finding of evidence suggestive of a possible association.

It is of interest to note that in a comparison of the risk factors for sinonasal and nasopharyngeal cancers, Zhu et al. (2002) report that smoking was a risk factor for squamous cell tumors at both sites. It is anticipated that ETS also would have similar effects in both sites.

As mentioned in our response to comments by M. LeVois, the results of the Yuan et al. (2000) study suggest a gender difference in cancer susceptibility in which females are more at risk for nasopharyngeal cancer after ETS exposure. For both males and females there is evidence of a dose-response for childhood exposure to both maternal and paternal smoking, although in males the confidence intervals include no effect. The study by Armstrong et al. (2000) did not find an association between nasopharyngeal cancer and ETS exposure in adulthood, but there was a significant association between childhood exposure to parental smoking and subsequent

nasopharyngeal cancer (OR 1.54; $p = 0.040$). This is consistent with the results of Yuan et al. for females and may indicate a developmental window of susceptibility. More recent studies suggest an association between childhood ETS exposure and subsequent development of nasopharyngeal cancer but leave the role of ETS exposure in adulthood undecided.

Section 7.4.1 Breast Cancer

Comment 3:

More weight should be given to the recent published findings from cohort studies in view of their large size and ability to clearly establish exposure as occurring before recognition of the cancers.

Response:

The recent cohort study by Reynolds et al. (2004) has been added to the review. Although cohort studies in general have the potential to be preferable for examination of risk, all of these studies suffer from seriously incomplete measures of passive smoking exposure. The potential impact of this serious shortcoming in exposure measurement is addressed by Rothman and Greenland (Modern Epidemiology, 2nd edition). A fundamental requirement for study validity is a level of accuracy in exposure ascertainment. In regards to the prospective studies of ETS and breast cancer, they have not to date included studies that have considered all of the sources of lifetime ETS exposure. In the literature on ETS and lung cancer, it is generally considered that the most influential study is that of Fontham et al (1994), which is a case-control study that represented the best exposure history in its design by including all relevant exposures, a large diverse population, and cotinine measurements for exposure assessment. While it is true that in the prospective studies exposure is ascertained prior to disease onset and that this is a desirable feature, exposure during the critical period of adolescence and young adulthood is obtained by retrospective history, since enrollment is typically well beyond that time in life. So, exposures that may be occurring during critical windows (e.g., peripubertal, prior to first pregnancy) for breast cancer are obtained retrospectively in both case-control and cohort studies, and the benefits of a prospective cohort study are thereby lessened. As well, typically the cohort studies identify exposure at a single timepoint at the onset of the cohort study which has been shown to have significantly reduced predictive value in a study of ETS and cardiovascular risk (Whincup et al., 2004). The problem of reporting bias related to retrospective studies is mitigated as the

potential link of smoking or ETS to breast cancer has not been well accepted in the scientific literature and is not commonly known to the public.

Comment 4:

The meta-analysis from the Collaborative Group Study of Breast Cancer, Alcohol, and Smoking used a simplistic characterization of active smoking in their analysis - ever/never and current/ex-smoker - however, it is not clear why this variable would be considered by the California EPA authors as "poor quality".

Response:

Comparing ever to never smokers (whether current or former) is a very crude estimate of exposure. There is no attempt to quantify the degree of exposure in this analysis. One of the paper's main limitations is the inability to consider in its analysis exposure to environmental tobacco smoke. The above mentioned pooled analysis makes no claims of considering passive smoke exposure in any way. Under the methods section they state; "no attention was given to the reported associations of breast cancer with environmental tobacco smoke exposure". If, as we believe to be true, the data support a relative risk of ETS that is in a range that approximates that of active smoking (for whatever reason), and if most non-smokers have had significant ETS exposure, which is certainly the case particularly in the many older studies included here, then it is not surprising that this analysis would be unable to identify a risk.

Additionally, several recent papers suggest positive associations emerging after 30- 40 years smoking duration (Terry and Rohan 2002, Johnson et al., 2003, Reynolds et al. 2004); association with years of smoking prior to first pregnancy (Band et al. 2002, Terry and Rohan 2002, Eagan et al. 2002, Johnson et al. 2003, Reynolds et al. 2004) or onset smoking at earlier age (Eagan et al. 2002, Calle et al. 1994, Reynolds et al. 2004). The analysis by the collaborative group is unable to account for these time-dependent associations noted in various studies.

Passive smoking has been shown to be associated with alcohol consumption (Reynolds et al. 2004, J Women's Health). In our analysis of passive smoking there is an associated risk that exceeds that identified with alcohol. Since the pooled analysis did not include information about passive smoking, it is unable to untangle the degree to which the reported association with

alcohol may in fact be due to its correlation with passive smoke exposure. Johnson (2000), Kropp and Chang-Claude (2002), Marcus (2000) and Morabia (1996) are examples of studies that found little or no modification of risk when adjusting for alcohol consumption.

Section 7.4.1.3 Active smoking and breast cancer.

Comment 5:

The first paragraph that precedes the discussion of individual studies appears to be a partial summary, but it does not synthesize the information and may be misleading. For example, it appears that positive findings that appear only in a subgroup are not labeled as such. The Egan study is said to show an association in either active or former smokers. However, that study showed no overall association of smoking and breast cancer among current smokers (RR=1.04) or ex-smokers (1.09) and so the authors probably were referring to active and former smokers among a subset of the women.

Response:

This sentence will be altered to read, “These studies indicated an increased risk, either overall or in some subgroupings...”.

Comment 6:

This section needs a synthesis that assesses the body of epidemiological evidence. Since the findings for the active smoking section presumably are included to provide evidence about the plausibility of the findings for passive smoking and to set the stage for discussions about consistency with ETS findings, there probably should be a synthesis section for each active smoking section with updated information/studies. The synthesis should clearly distinguish overall findings for smoking and breast cancer from findings in specific subgroups.

Response:

Additional discussion and summary have been included under section 7.4.2.5.1, Relative Potency of Active and Passive Smoking. The tables included in the active smoking section do present overall findings as well as those for various subgroupings. As you note, the main purpose of including the active smoking studies was to inform the discussion of passive smoking in light of the widely held belief that the accumulating data associated with passive smoking was inconsistent with active smoking data. The addition of Reynolds et al. (2004), a U.S. based cohort study, has further strengthened the evidence that active smoking is in fact associated with

increased risk as well as passive smoking. Since the discussion was included as supportive evidence, a less complete discussion of active smoking has been presented in the document.

Section 7.4.1.4. ETS and breast cancer.

Section 7.4.1.5.

Comment 7:

A new study that could be included here is: Gammon MD et al., Environmental tobacco smoke and breast cancer incidence. To be published in Environmental Research in 2004, but available now through Science Direct.

Response:

Thank you. This new study has been added.

Comment 8:

The citation to Terry et al., 2002 on page 7-122 is incorrect. This study does not address passive smoking and breast cancer, only active smoking.

Response:

Thank you. This has been corrected and moved to the appropriate section on active smoking.

Comment 9:

There is a reference to a paper by Zhao in 1999 in Table 7.4F. However, this study is not described in text and the reference does not appear in the list of references.

Response:

Thank you. A description of the study has been added.

Section 7.4.1.6.

Comment 10:

This section is labeled as a summary of the evidence regarding ETS, but it focuses only on the possible explanations of findings reported in the previous CalEPA report and does not address findings since then. Have the limitations to the interpretation of the findings in the previous CalEPA report been fully addressed in the more recent studies?

Response:

This section (as well as several subsections under it) has been expanded and relabeled to more accurately identify topics discussed. “Limitations of the studies” has an expanded discussion. It is our premise that many of the limitations of the previous studies reviewed in the 1997 document have been well addressed in the studies subsequently and particularly in those categorized by us as “unlikely to have missed important measures of ETS exposure” in Table 7.4.1R of the current version.

Comment 11:

Overall risks associated with passive smoking and dose response relationships should be summarized, then focus on subsets (e.g., pre- and post-menopausal), providing risks for the subset and, where available, dose-response relationships for that subset.

Response:

We have done this in the report, primarily by summarizing the data in tables and noting in the text when there was evidence of effect in specific subsets and evidence of dose-response.

Section 7.4.1.7: Consistency. (Starting on page 7-136)

Comment 12:

This section addresses the qualities of the most recent studies, not the consistency among them. To address consistency this section should include an evaluation of agreement among the studies of ETS, including across subgroups defined by biological characteristics (e.g., menopausal status) as well as the consistency with findings for active smoking as well as the consistency of findings within studies that examined both active and ETS.

Response:

Consistency refers to repeated observation of an association in different populations under different circumstances (Rothman and Greenland 1998). We are aware that total consistency of findings across studies is both difficult to evaluate (due to differing methodologies as well as random errors) and difficult to present since metrics evaluating exposure and risk vary from study to study. As the causal mechanism is not fully elucidated, studies have investigated various

hypotheses. According to Rothman and Greenland (1998), “Consistency is apparent only after all the relevant details of a causal mechanism are understood, which is to say very seldom.”

Despite these difficulties, this section summarizes some of the ways in which repeated associations between environmental tobacco smoke exposure and development of breast cancer have been demonstrated over time and across studies in different countries. We have attempted to further demonstrate the increased consistency of findings when studies have done a better job of measuring lifetime ETS exposure (presented in figure 7.4.2).

Overall, in our analysis, the studies of breast cancer are a heterogeneous group. When we restrict the studies to those with better exposure measurements (including childhood, adult residential and workplace exposures), the test for homogeneity is consistent with a homogeneous grouping and the risk estimates are higher.

Section 7.4.1.7: Strength and specificity.

Comment 13:

Recommend addressing overall risks associated with passive smoking and the dose-response relationships curve overall, then focus on subsets of women (e.g. pre and post menopausal) providing the risks for the subset and the dose response for that subgroup, if available. This is an important distinction because a finding that is homogenous across subgroups and shows a dose response relationship must have a different biological mechanism than one that is confined to women with particular biological characteristics (e.g., particular types of tumors, women with particular biological characteristics such as menopausal status).

Response:

We have done this in the report, primarily by summarizing the data in tables and noting in the text when there was evidence of effect in specific subsets and evidence of dose-response.

We do not agree with the premise in the last sentence. The response of breast cancer risk to ETS exposure appears both in the overall data and in the various subgroups. The degree of response may vary between subgroups, so that it is more likely that a statistically significant effect will be observed in the more sensitive subgroups. However, we do not see any indication of absolute non-responsiveness in certain subgroups, and have therefore not emphasized this type of analysis.

Table 7.4.G.

Comment 14:

Add a table on post-menopausal findings. This would be useful for assessing consistency of findings.

Response:

A table will be added to the final report and provided to the Scientific Review Panel.

References:

Rothman KJ, Greenland S. (1998) Modern Epidemiology, second edition. Lippincott-Raven Publishers, Philadelphia.

Whincup PH, Gilg JA, Emberson JR, Jarvis MJ, Feyerabend C, Bryant A, Walker M, Cook DG (2004). Passive smoking and risk of coronary heart disease and stroke: prospective study with cotinine measurement. BMJ. Jul 24;329(7459):200-5.

These and other references noted are cited in the document.